Practical Radiation Oncology (2018) **8**, 28-39

practical radiation oncology
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Basic Original Report

Prostate cancer–specific PET radiotracers: A review on the clinical utility in recurrent disease

Jaden D. Evans MD [a,1], Krishan R. Jethwa MD [a,1], Piet Ost MD, PhD [b], Scott Williams MD [c], Eugene D. Kwon MD [d], Val J. Lowe MD [e], Brian J. Davis MD, PhD, FABS [a,*]

[a]*Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota*
[b]*Department of Radiation Oncology and Experimental Cancer Research, Ghent University Hospital, Ghent, Belgium*
[c]*Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*
[d]*Department of Urology, Mayo Clinic, Rochester, Minnesota*
[e]*Department of Radiology, Mayo Clinic, Rochester, Minnesota*

Received 9 June 2017; revised 12 July 2017; accepted 18 July 2017

Abstract Prostate cancer–specific positron emission tomography (pcPET) has been shown to detect sites of disease recurrence at serum prostate-specific antigen (PSA) levels that are lower than those levels detected by conventional imaging. Commonly used pcPET radiotracers in the setting of biochemical recurrence are reviewed including carbon 11/fludeoxyglucose 18 (F-18) choline, gallium 68/F-18 prostate-specific membrane antigen (PSMA), and F-18 fluciclovine. Review of the literature generally favors PSMA-based agents for the detection of recurrence as a function of low PSA levels. Positive gallium 68/F-18 PSMA positron emission tomography/computed tomography scans detected potential sites of recurrence in a median 51.5% of patients when PSA level is <1.0 ng/mL, 74% of patients when PSA level is 1.0 to 2.0 ng/mL, and 90.5% of patients when PSA level is >2.0 ng/mL. Review of carbon 11/fludeoxyglucose 18 (F-18) choline and F-18 fluciclovine data commonly demonstrated lower detection rates for each respective PSA cohort, although with some important caveats, despite having similar operational characteristics to PSMA-based imaging. Sensitive pcPET imaging has provided new insight into the early patterns of disease spread, which has prompted judicious reconsideration of additional local therapy after either prostatectomy, definitive radiation therapy, or postprostatectomy radiation therapy. This review discusses the literature, clinical utility, availability, and fundamental understanding of pcPET imaging needed to improve clinical practice.

Supplementary material for this article (https://doi.org/10.1016/j.prro.2017.07.012) can be found at www.practicalradonc.org.
Conflicts of interest: None.

* Corresponding author. Department of Radiation Oncology, Mayo Clinic, 200 1st Street SW, Rochester, MN 55905.
E-mail address: Davis.Brian@mayo.edu (B.J. Davis).

[1] J.D.E. and K.R.J. contributed equally to this work.

https://doi.org/10.1016/j.prro.2017.07.011

Introduction

Prostate cancer remains 1 of the most common malignancies affecting men worldwide.[1,2] Prostate cancer recurrence following primary treatment is usually signaled by a rising serum prostate-specific antigen (PSA) level, which can be quite anxiety-provoking for patients and clinicians.[3-5] Fortunately, advances in prostate cancer–specific positron emission tomography (pcPET) have demonstrated new insights into patterns of disease recurrence.[6-8] Emerging pcPET radiotracers including carbon 11 (C-11) choline, gallium 68 (Ga-68) prostate specific membrane antigen (PSMA), C-11 acetate, and 18F-fluorocyclobutane-1-carboxylic acid fluciclovine (FACBC) provide opportunities to localize prostate cancer recurrence at an earlier state in the disease course when the PSA level is low, to inform medical decision-making, and to study PET-directed local therapy.[9-13]

In anticipation of increased use and availability of pcPET radiotracers, a critical review of the following is of interest: (1) fundamentals of PET; (2) current systematic reviews and meta-analyses of commonly used pcPET radiotracers; (3) comparative studies evaluating pcPET radiotracers; (4) US Food and Drug Administration (FDA) approval and availability; and (5) future directions of pcPET technology in the management of prostate cancer. We limit the scope of our discussion to pcPET radiotracers that image both soft tissue and bone and do not address other novel methods such as F-18 sodium fluoride PET or the use of whole body magnetic resonance imaging (MRI).

Methods and materials

A comprehensive literature search was performed using electronic databases, including: MEDLINE, EMBASE, PubMed, ScienceDirect, Web of Science, Cochrane Library, and Google Scholar. Search keywords included, but were not limited to: prostate, prostate cancer, prostate malignancy, prostate recurrence, recurrent prostate cancer, biochemical recurrence, positron emission tomography, PET, prostate specific membrane antigen, PSMA, choline, C-11 or F-18 choline PET, C-11 acetate PET, fluciclovine, FACBC, and Axumin. Additional articles were identified by searching bibliographies of relevant literature.

Discussion

Fundamentals of PET

PET is a type of functional imaging technique used to localize metabolic processes. A radionuclide produced from either a cyclotron or a generator is attached to a biologically active molecule forming a PET radiotracer. The PET radiotracer is then introduced into the patient by injection, ingestion, or inhalation. In modern practice, the functional information from PET is almost always acquired simultaneously with anatomic information provided via computed tomography (CT) scanning or MRI. Once the PET radiotracer is administered, the patient is positioned so that detectors can register incident gamma rays, 2 511 keV photons traveling in opposite directions, produced as the radionuclide decays resulting in an annihilation event from a positron combining with an electron after traversing a short distance. The detector's electronics are synced in such a way that the 2 photons emitted are detected on opposite sides and are called coincident and therefore must have originated from the same annihilation event. These coincident projections are assigned to a line of response and are then reconstructed using standard tomographic techniques to identify the location of the annihilation event. By using modern "time of flight" information in PET image reconstruction with very fast scintillators, the origin of the annihilation event along the line of response is detected with improved accuracy.[14] More recent advancements in PET imaging and spatial resolution have been further improved by the use of iterative reconstruction algorithms such as the Ordered Subsets Expectation Maximization and Bayesian penalized-likelihood reconstruction algorithms.[15] Newer reconstruction algorithms have mean standardized uptake value levels 2 to 3 times higher than conventional Ordered Subsets Expectation Maximization technology, which should be considered when comparing studies of intergenerational scanners.[16] Properties of important pcPET radiotracers are shown in Table 1.[17]

Table 1 Properties of important prostate cancer–specific positron emission tomography radiotracers

Isotope	Half-life (min)	Production method
Carbon 11 (^{11}C)	20.3	Cyclotron
Gallium 68 (^{68}Ga)	67.7	Generator/cyclotron
Fluorine 18 (^{18}F)	109.8	Cyclotron
Copper 64 (^{64}Cu)	762.1	Cyclotron

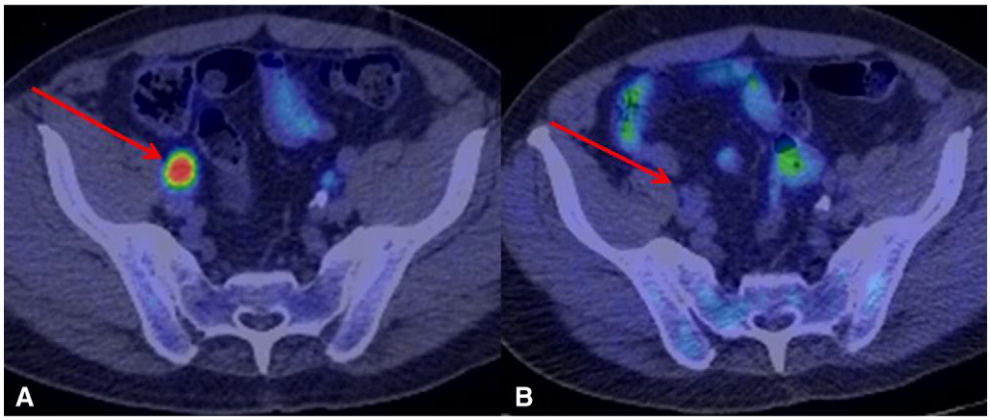


Figure 1 Carbon 11 (C-11) choline positron emission tomography/computed tomography scan of a 75-year-old man status post radical prostatectomy for prebiopsy prostate-specific antigen (PSA) 5.3 ng/mL, Gleason 8, pT2c,N0,M0, R0 resection who experienced a rising PSA postoperatively to 0.55 ng/mL and was treated with salvage prostatic fossa only radiation therapy in 7 months later. PSA nadir after salvage radiation therapy was 0.7 ng/mL. PSA rose quickly to 5.2 ng/mL and patient was referred for C-11 choline (A), which showed a choline-avid right external iliac lymph node. After 4 months of chemohormonal therapy with 6 cycles of docetaxel and 4 months of leuprolide acetate, the patient presented for repeat C-11 choline at which time PSA was <0.10 ng/mL (B). The patient then received a course of concurrent androgen suppression and consolidative radiation therapy to the pelvic lymph nodes, including simultaneous integrated boost to the prechemohormonal prostate cancer–specific positron emission tomography avid lymph node, with radiation portals abutting his previously irradiated prostatic fossa. The patient's PSA remains undetectable (<0.10 ng/mL) with no evidence of disease on follow-up imaging 2 years posttreatment.

Prostate cancer–specific PET scans are performed uniquely. Unlike standard F-18 PET scans, which are usually imaged starting at the head and scan toward the feet, pcPET scans typically image the pelvis first. Imaging is initiated 3 to 5 minutes after radiotracer administration and scanning begins at the mid-thigh and proceeds to the base of skull. This is done primarily to minimize urinary tract contamination, but also because of the short half-life

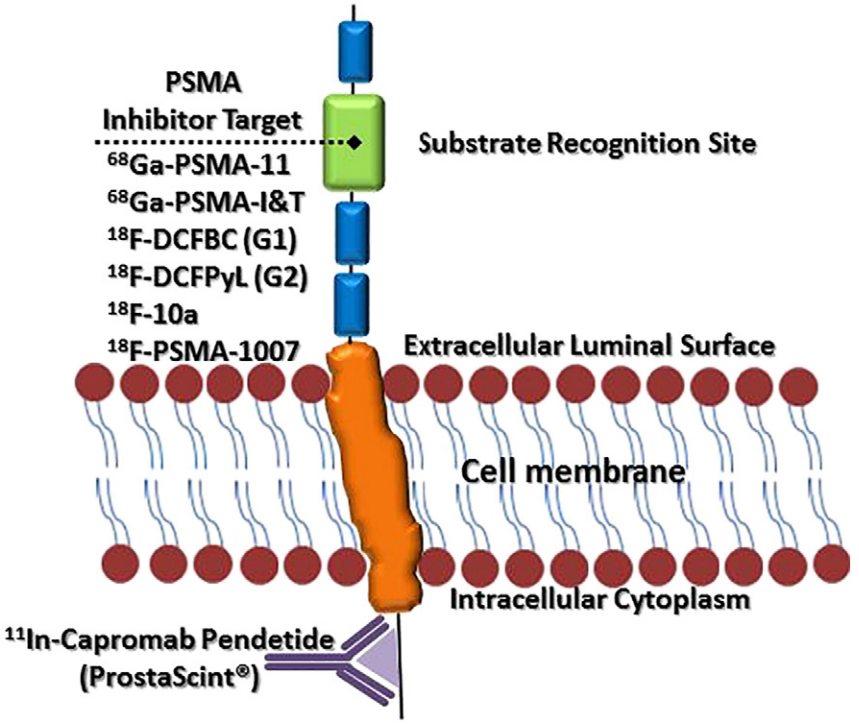


Figure 2 Prostate-specific membrane antigen (PSMA) structure with common PSMA small-molecule inhibitors that target the substrate recognition site that are combined with a radioisotope to form a clinically useful pcPET radiotracer. Common Ga-68 PSMA radiotracers as well as first- (G1) and second-generation (G2) F-18 PSMA radiotracers are shown. Promising experimental radiotracers currently being investigated have also been included. ProstaScint targets the short intracellular domain.

of isotopes such as C-11. Urinary tract contamination is the primary reason pcPET protocols are performed in this manner, including those involving radiotracers with longer half-lives such as F-18 fluciclovine.

Background for choline, PSMA, and fluciclovine

This review will focus on 3 PET radiotracers of interest: C-11/F-18 choline, Ga-68/F-18 PSMA, and F-18 fluciclovine.

Choline metabolism has been shown to be altered in prostate cancer cells. Increased levels of choline compounds concentrate preferentially in human prostate cancer cells derived from metastases.[18] Alteration of choline metabolites within the cancer cell relates to choline transport, incorporation, and utilization within the cell.[19-21] Preclinical data conflict on the theory of augmented choline use by the cell because of increased cell membrane synthesis and proliferation.[18,22,23] Multiple metabolomic studies on prostate cancer have shown permutations in choline metabolism not related to cell membranogenesis[23]; however, it is well accepted that choline is used via a 3-step process known as the Kennedy pathway for the de novo synthesis of phosphatidylcholine, which is an essential component of the cell membrane.[24] Preclinical data have shown that there is an increase in the expression of choline transporters and an increase in the choline transport rate in malignant prostate cells when compared with normal prostate tissues.[25] Interestingly, preclinical data have also shown that treatment of prostate cancer cells leads to changes in energetic metabolism and choline metabolism.[26] This notion is consistent with what experienced centers have observed after administration of systemic therapy to patients with C-11/F-18 choline PET-positive lymph node(s), wherein the nodes are no longer choline-avid (Fig 1).

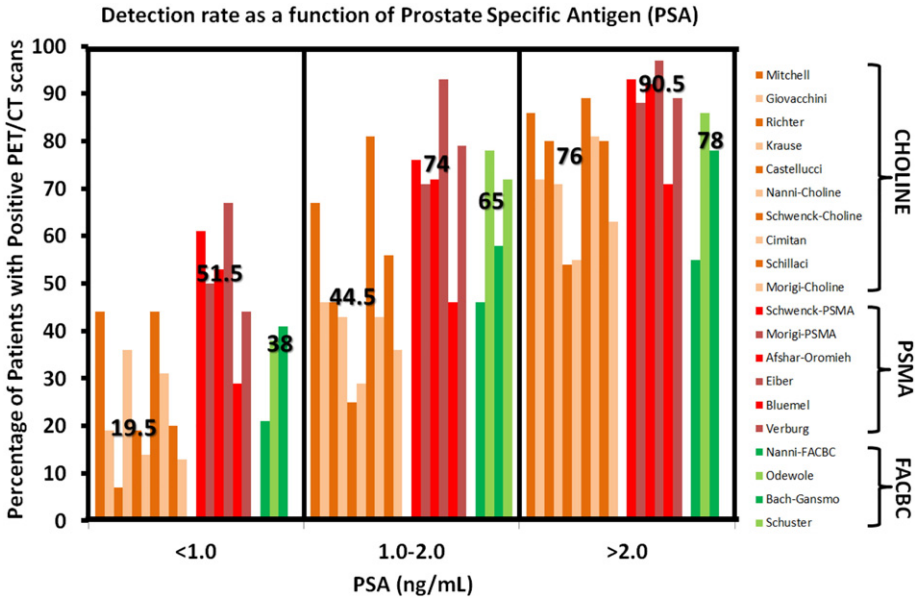
PSMA is highly overexpressed in prostate cancer cells as a transmembrane protein.[27] PSMA is a folate hydrolase cell surface glycoprotein expressed in a number of different tissue types, including other cancers, but benign processes as well. Before malignant transformation has occurred, PSMA is localized to the cytoplasm and apical side of the prostate epithelium that lines prostatic ducts.[28] The function of cytoplasmic PSMA is not fully understood; however, as malignant transformation occurs, PSMA is transferred to the luminal surface of the prostatic ducts.[28] PSMA expression has been shown to be widespread in most prostate tumors even when PSA staining is negative or weak.[29] Increased PSMA expression has also been observed when the cell becomes castrate-resistant.[30] As a result, PSMA has emerged as 1 of the most favorable targets for PET imaging. Prostate cancer PSMA overexpression has been shown to be 100- to 1000-fold that of normal tissue expression; furthermore, PSMA expression may increase as tumor grade and castrate resistance increases.[31,32] PSMA is hypothesized to have a transport function because it internalizes ligands similar to J591, a monoclonal antibody that targets the extracellular domain. In general, targeted antibodies have presented challenges as diagnostic radiopharmaceuticals with their long circulating half-life and resultant high nonspecific background-to-tumor noise. Consequently, the more recent focus of PSMA radiopharmaceutical development has focused on small-molecule inhibitors

Table 2 Summary of sensitivity and specificity of meta-analyses evaluating PSMA, choline, and fluciclovine PET/CT

Systematic review and meta-analysis	No. of studies	No. of patients	Sensitivity (per lesion) (95% CI)	Specificity (per lesion) (95% CI)	Sensitivity (per patient) (95% CI)	Specificity (per patient) (95% CI)
PSMA						
Perera[10]	N = 16	N = 1309	80% (66-89)	97% (92-99)	86% (37-98)	86% (3-100)
Choline						
Fanti[54]	N = 12	N = 1270			89% (83-93)	89% (73-96)
Evangelista[55]	N = 19	N = 1555	86% (83-88)	93% (90-95)		
Umbehr[56]	N = 12	N = 1055	90% (74-97)	95% (92-97)	85% (79-89)	88% (73-95)
Shen[57] (bone metastases)	N = 9	N = 423	83% (81-85)	95% (94-97)	87% (79-93)	97% (93-99)
Fluciclovine						
Ren[59]	N = 6	N = 251			87% (80-92)	66% (56-75)[a]

CI, confidence interval; CT, computed tomography; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

[a] Meta-analysis did not include 2 recent studies evaluating operational characteristics for F-18 fluciclovine specificity. Specificity may be higher than reported.



Study	PET Radiotracer	% of Patients with BCR	% of Patients with Positive PET/CT		
			PSA <1.0	PSA 1.0-2.0	PSA >2.0
Choline					
Mitchell[65]	C-11 Choline	100% (176/176)	44% (15/34)	67% (21/31)	86% (96/111)
Giovacchini[81]	C-11 Choline	100% (358/358)	19% (27/141)	46% (39/85)	72% (95/132)
Richter[82]	C-11 Choline	100% (73/73)	7% (1/15)	46% (6/13)	80% (36/45)
Krause[83]	C-11 Choline	100% (63/63)	36% (8/22)	43% (3/7)	71% (24/34)
Castellucci[84]	C-11 Choline	100% (190/190)	19% (10/51)	25% (10/39)	54% (54/100)
Nanni[66]	C-11 Choline	100% (89/89)	14% (4/28)	29% (8/28)	55% (18/33)
Schwenck[69]	C-11 Choline	100% (101/101)	44% (8/18)	81% (21/26)	89% (51/57)
Cimitan[85]	F-18 Choline	100% (1000/1000)	31% (66/211)	43% (66/153)	81% (513/636)
Schillaci[86]	F-18 Choline	100% (49/49)	20% (2/10)	56% (5/9)	83% (25/30)
Morigi[67]	F-18Methchol	100% (38/38)	13% (2/16)	36% (5/14)	63% (5/8)
PSMA					
Schwenck[69]	Ga-68 PSMA	100% (101/101)	61% (11/18)	76% (20/26)	93% (53/57)
Morigi[67]	Ga-68 PSMA	100% (38/38)	50% (8/16)	71% (10/14)	88% (7/8)
Afshar-Oromieh[87]	Ga-68 PSMA	100% (319/319)	53% (27/51)	72% (28/39)	92% (204/221)
Eiber[88]	Ga-68 PSMA	100% (248/248)	67% (35/52)	93% (67/72)	97% (120/124)
Bluemel[89]	Ga-68 PSMA	100% (32/32)	29% (4/14)	46% (5/11)	71% (5/7)
Verburg[90]	Ga-68 PSMA	100% (155/155)	44% (12/27)	79% (15/19)	89% (97/109)
Fluciclovine					
Nanni[66]	F-18 FACBC	100% (89/89)	21% (6/28)	46% (13/28)	55% (18/33)
Odewole[63]	F-18 FACBC	100% (53/53)	38% (3/8)	78% (7/9)	86% (31/36)
Bach-Gansmo[91]	F-18 FACBC	100% (596/596)	41% (53/128)	58% (N?)	75-85% (N?)
Schuster[62]	F-18 FACBC	100% (93/93)		72% (N?)	

Figure 3 Summary of data evaluating pcPET detection rates as a function of PSA. All patients included in the analysis had biochemical recurrence. General trend favors PSMA across all PSA levels. FACBC, 18F-fluorocyclobutane-1-carboxylic acid fluciclovine. Other abbreviations as in Fig 1.

that target the active substrate recognition site (Fig 2). Eder et al first described the most commonly used PSMA inhibitor in PET imaging, Ga-68 PSMA-HBED-CC, also known as Ga-68 PSMA-11, which also is internalized and accumulates in high levels even in small metastases.[28,33]

There appears to be growing interest in developing an 18-F–labeled PSMA agent. Some experts argue that it would offer advantages with respect to availability, production amount, and image resolution. This approach was first explored at Johns Hopkins University where F-18 DCFBC, the first-generation F-18 PSMA radiotracer, was

developed and is currently licensed to Cyclotek for clinical use in Australia and New Zealand.[34,35] Since the development of F-18 DCFBC, second-generation tracers such as F-18 DCFPyL have been developed.[36] Currently, there are a number of groups working to develop the most clinically useful next-generation F-18–labeled PSMA radiotracer.[37-42] PSMA's unique expression differential between cancer and normal cells coupled with its large extracellular domain provides an excellent target for imaging, but also for therapeutics such as theranostic applications with lutetium 177 PSMA. Less than 10% of prostate cancers have no uptake on PSMA PET.[43] Additionally, the short half-life of Ga-68 (68 minutes) results in low radiation exposure to patients. Furthermore, the agent is rapidly cleared from nontarget tissue. On average, patients receive 3.0 mSv from the PET component of 150 MBq of Ga-68-PSMA-11, which is lower than most other pcPET agents such as C-11 and 18-F choline scans.[44,45]

Fluciclovine is a synthetic amino acid, and an analog of L-leucine, which is preferentially taken up by prostate cancer cells and gliomas via specialized amino acid transporters, namely alanine-serine-cysteine transporter 2 (ASCT2) and LAT-1.[46-50] Its chemical name is anti-1-amino-3-FACBC, and is commonly known by its trade name Axumin. Amino acid transporters such as ASCT2 play a critical role in amino acid metabolism in prostate cancer cells. ASCT2 is an important transporter of glutamine, which is known to be an essential tumor nutrient and has been implicated in cancer signaling pathways.[51,52] Fluciclovine is predominantly transported by ASCT2 and transports in a manner similar to glutamine.[53] Unlike glutamine, however, 18-F fluciclovine does not undergo additional metabolism in the cell, which lends to its intracellular accumulation particularly in prostate cancer cells and at major sites of amino acid metabolism such as the liver and pancreas.[54]

Additional pcPET radiotracers used in prostate cancer imaging have been developed as previously noted. These include C-11 acetate and F-18 sodium fluoride. In addition, F-18 PET may be useful in imaging prostate cancer patients who have developed dedifferentiated neuroendocrine tumors of the prostate,[55] which conversely may not image well using these pcPET agents.

Operational characteristics of PET radiotracers

In recent years, numerous systematic reviews and meta-analyses have been published evaluating the pooled operational characteristics of various pcPET radiotracers in the setting of prostate cancer recurrence (Table 2). These reports are often analyzed on a per-patient or per-lesion basis. Caution should be exercised in interpreting sensitivities and specificities because a comparative gold standard such as histologic confirmation is not always available. The focus of this review is recurrent disease; consequently, operational characteristics are emphasized in the setting of biochemical recurrence after definitive treatment. The use of these pcPET agents in initial staging, response to therapy, and radiation therapy planning are of great interest but beyond the scope of this review. Ga-68 PSMA was recently evaluated by Perera et al, in which 16 articles including 1309 patients were evaluated.[10] When evaluating on a per-patient basis, the summary sensitivity and specificity were identical at 86%. When analyzed on a per-lesion basis, summary sensitivity was 80% and specificity was 97%. Additionally, it was noted that patients with biochemical recurrence had increasingly positive Ga-68 PSMA PET scans as the pre-PET PSA increased. They found that 58% were positive at a pre-PET PSA of 0.2 to 1 ng/mL, which increased to 76% with a PSA of 1 to 2 ng/mL and further increased to 95% for PSA >2 ng/mL.

C-11 choline was also recently evaluated by Fanti et al, specifically looking at its ability to detect sites of recurrence in the setting of biochemical recurrence after definitive treatment.[56] There were 12 studies including 1270 patients to derive a pooled sensitivity and specificity of 89%. This was similar to previously published meta-analyses by Evangelista et al, Umbehr et al, and Shen et al,[57-59] although these reports included both C-11 and F-18 choline studies. Fanti et al highlight the accuracy of C-11 choline PET at different sites of recurrence, reporting a decreased pooled sensitivity of 61% for detection of local recurrence. This result is consistent with comparative studies that have shown multiparametric MRI with endorectal coil to be superior to C-11 choline for the detection of local recurrence, whereas C-11 choline PET/CT was shown to be superior to MRI for pelvic lymph node metastases and equal with respect to bone metastases.[60]

F-18 fluciclovine was evaluated by Ren et al and included 6 studies including 251 patients with biochemical recurrence.[61] The pooled sensitivity and specificity on a per-patient analysis was 87% and 66%, respectively; however, caution should be exercised when interpreting the specificity in this meta-analysis. Two recent important papers evaluating the operational characteristics of F-18 fluciclovine were not included in this analysis. Schuster et al reported specificities of 40% and 97% for prostate bed and extraprostatic lesions, respectively.[62] Odewole et al similarly demonstrated specificities of 56% and 100% for prostate bed and extraprostatic lesions, respectively.[63] These data indicate that the specificities may be higher than the meta-analysis suggests, particularly for extraprostatic disease.

Important factors to consider when interpreting operational characteristics of various pcPET radiotracers include the reference standard used to establish positive and negative proof, particularly with respect to extraprostatic disease, because these sites can be challenging to obtain histologic confirmation. Furthermore, whether the

PSMA
- Johns Hopkins University, Baltimore, MD
- Mayo Clinic, Rochester, MN
- MSKCC, New York, NY
- RITA Foundation, Houston, TX
- Stanford, Palo Alto, CA
- UCLA, Los Angeles, CA
- UCSF, San Francisco, CA
- University of Wisconsin, Madison, WI

CHOLINE
- Decatur Memorial Hospital, Decatur, IL
- Mayo Clinic, Rochester, MN
- MSKCC, New York, NY
- The Queen's Medical Center, Honolulu, HI
- UCSF, San Francisco, CA
- University of Michigan, Ann Arbor, MI
- Wake Forest University, Winston-Salem, NC
- Washington University, St. Louis, MO

FLUCICLOVINE
- Cedars-Sinai Medical Center, Los Angeles, CA
- City of Hope, Duarte, CA
- Coastal Urology Associates, Brick, NJ
- Emory University, Atlanta, GA
- Fox Chase Cancer Center, Philadelphia, PA
- Genesis Research, LLC, San Diego, CA
- Loyola University, Maywood, IL
- Manhattan Medical Research, New York, NY
- Mount Sinai Hospital, New York, NY
- Thomas Jefferson, Philadelphia, PA
- Tower Urology, Los Angeles, CA
- University of Florida, Jacksonville, FL
- University of Louisville, Louisville, KY
- University of Pennsylvania, Philadelphia, PA
- University of Utah, Salt Lake City, UT
- Urologic Consultants, Bala Cynwyd, PA
- VA Medical Center, Indianapolis, IN
- Washington University, St. Louis, MO

Figure 4 These are the locations of prostate cancer-specific PET scanners across the United States as of 2017. Abbreviations as in Fig 3.

analysis was performed on a per-patient or per-lesion basis provides additional insight into the interpretation of data. For example, many studies relied on histologic confirmation per-patient for positivity of extraprostatic disease, given it would be impractical to sample every PET avid site, whereas studies that used a per-lesion analysis often used a nonhistologic method of disease confirmation, which is subject to study examination bias.[64]

Detection rates as a function of PSA

PSA is routinely followed in prostate cancer patients after definitive treatment; however, the optimal timing of pcPET imaging is often debated amongst providers in the setting of a rising PSA after definitive treatment. Data regarding detection rates as a function of PSA are summarized in Fig 3. Reviews of 10 choline, 6 PSMA, and 4 fluciclovine studies evaluating detection rates as a function of PSA are shown. The median percentage of patients with positive pcPET scans is shown as the bolded number over each histogram cluster. The general trend suggests Ga-68 PSMA is superior to both C-11/F-18 choline and F-18 fluciclovine in detecting recurrence at PSA levels <2.0 ng/mL.

There are important caveats to this comparative review, however. First, the fluciclovine data are limited by few data points. Second, the dose of radiotracer varies greatly between studies and consequently effects sensitivity, specificity, and detection rates. For example, in the study by Mitchell et al, in which detection rates were relatively high, the C-11 choline dose ranged from 555 to 740 MBq.[65] This dose was significantly greater than the choline dose given in prospective comparative studies that showed lower choline PET detection rates, which often used 3.4 to 3.5 MBq/kg.[66,67] For an 80-kg patient, this computes to 280 MBq, essentially half the dose used in the

Mitchell et al study. Finally, the selection of radioisotope, such as Ga-68 versus F-18 PSMA, and the use of advanced iterative reconstruction algorithms will inevitably influence detection rates in the future, which are important details not always addressed in related studies. Nevertheless, the general trend of these data presented in Fig 3 suggests superiority with PSMA particularly at PSA levels <1 ng/mL. Prospective studies comparing PSMA to choline and/or fluciclovine PET/CT are currently under way.

Comparative investigations of PET radiotracers

A prospective study by Morigi et al compared Ga-68 PSMA with F-18 fluoromethylcholine.[67] The findings from this study were that Ga-68 PSMA was better than F-18 fluoromethylcholine in patients with biochemical failure. It should be noted, however, that this study used low administered choline doses (3.5 MBq/kg) and a slightly different radioisotope, F-18 fluoromethylcholine, as opposed to C-11 choline. Additional data comparing PSMA to choline come from retrospective series. Afshar-Oromieh et al evaluated 37 patients with biochemical recurrence that underwent scans with both F-18 fluoromethylcholine and Ga-68 PSMA PET/CT within 30 days of 1 another.[68] The authors concluded that PSMA offered a higher detection rate, higher maximum standardized uptake value, and higher tumor-to-background ratio when compared with the F-18 fluoromethylcholine scan. Schwenck et al retrospectively compared Ga-68 PSMA-11 with C-11 choline[69] and demonstrated a higher detection rate with PSMA. Interestingly, however, of the 67 patients with biochemical recurrence, 458 lymph node metastases were detected. Although 39% were exclusively identified with Ga-68 PSMA, there were 6% identified with C-11 choline only, and the majority (55%) were identified by both. The advantage of PSMA, and the clinical situation in which the majority of PSMA-only detection took place, was in patients presenting with PSA levels <1 ng/mL.

Comparisons between F-18 FACBC and C-11 choline have largely been undertaken by Nanni et al. Before 2016, 3 preliminary studies comparing these 2 imaging modalities in patients with biochemical recurrence were published.[70-72] These studies reported favorable detection rates for fluciclovine compared with choline and provided background for the publication of their prospective trial.[66] The authors showed that, in patients with biochemical relapse after prostatectomy, F-18 FACBC had higher sensitivity and specificity compared with C-11 choline (37% and 67% vs 32% and 40%). They emphasized that F-18 FACBC had better true-positive findings at lower PSA levels (<1 ng/mL) with 6/28 (21%) patients with F-18 FACBC versus 4/28 (14%) patients with C-11 choline. A major limitation of this trial, and a limitation of many imaging studies evaluating operational characteristics, is the use of a suboptimal reference standard. The standard of reference in this particular study was reevaluation of the clinical and imaging history after following patients for an average of 1 year. In some cases, this meant histologic confirmation including 31% (4/13) of patients with positive local relapse, 15% (4/26) of patients with positive lymph nodes, and 0% (0/7) of patients with positive bone lesions. For most cases, however, the standard of reference was by repeat imaging or PSA trend after therapy. Furthermore, a low choline dose (3.4 MBq/kg) was administered, which may limit the study's generalizability particularly for centers that use higher choline doses.

There have been no direct comparisons between fluciclovine and Ga-68/F-18 PSMA to date. Schuster et al prospectively evaluated patients with biochemical recurrence comparing F-18 FACBC against indium 111 capromab pendetide (ProstaScint), a radiolabeled monoclonal antibody that binds to PSMA.[62] This study showed FACBC performed better than ProstaScint, demonstrating FACBC's superiority in detecting more prostatic and extraprostatic disease and effectively upstaging 25% of patients. A major strength of this study was the high incidence of pathologic confirmation of true positives, with 96% (74/77) of index lesions histologically confirmed including 55 prostate bed and 22 extraprostatic lesions.

Availability and FDA approval

Currently there are 2 pcPET radiotracers that have gained FDA approval in the United States for the indication of identifying recurrent prostate cancer. C-11 choline received FDA approval on September 12, 2012, for the indication of PET imaging of patients with suspected prostate cancer recurrence.[73] F-18 FACBC received FDA approval on May 27, 2016, for prostate cancer patients with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.[74] Ga-68 PSMA has not yet received FDA approval. ProstaScint, indium-111 capromab pendetide, has gained FDA approval for its use in the evaluation of patients with newly diagnosed, biopsy-proven prostate cancer thought to be clinically localized but high risk for pelvic lymph node metastasis. Given the growing body of literature regarding the clinical utility of choline, fluciclovine, and PSMA, availability around the United States is rapidly expanding (Fig 4). Sites that provide choline scans are mostly C-11. Exceptions include the University of Michigan and The Queen's Medical Center in Honolulu, Hawaii, both of which offer F-18 choline scans. Sites that provide PSMA scans are mostly Ga-68 except for Johns Hopkins University and University of Wisconsin, both of which are evaluating F-18 PSMA scans.

In many parts of Europe, Asia, and Australia, pcPET radiotracers have made their way into widespread clinical practice. Some have argued that the current FDA regulation of PET radiotracers has been too prohibitive and stifling to the innovative process. Such limitations are

not as common in other parts of the world, particularly in Europe and Australia, where much of the innovation and data in pcPET radiotracers have been generated. Widespread international availability has led to multi-institutional prospectively controlled trials that accrue quickly and, in turn, are rapidly advancing the science of functional imaging. As a result, robust data are forthcoming and essential to determine how best to use this technology.

Clinical application of prostate cancer–specific PET imaging

Patients with a rising PSA after definitive therapy often ask the clinically relevant question, "Where is the origin of my rising PSA?" Before the advent of widespread clinical use of pcPET radiotracers and multiparametric MRI, clinicians relied on suboptimal tools, primarily bone scans and CT scans, to explore the answer to this question. As shown in Fig 3, pcPET radiotracers are able to detect sites of recurrence when the PSA level is low, even PSA levels <1.0 ng/mL. By comparison, bone scans detect osseous metastases at a median PSA level of 40 ng/mL.[75] Abuzallouf et al reviewed 23 studies evaluating bone scans in newly diagnosed cases of prostate cancer and showed osseous detection rates of 2.3% for PSA <10 ng/mL, 5.3% for PSA 10.1 to 19.9 ng/mL, and 16.4% for PSA 20.0 to 49.9 ng/mL.[76] In the same review, 25 studies evaluating CT scans found lymph node metastases in 0% of patients with PSA <20 ng/mL and 1.1% of patients with PSA >20 ng/mL. Additional evidence from a prospective population-based analysis of newly diagnosed prostate cancer showed CT scan detection rates were <15% for patients with PSA levels between 4 and 20 ng/mL.[77] Based on these poor positive yields, the overall use of bone scan and CT imaging has declined in pretreatment evaluation, which has also translated to limited use in the recurrent setting.[78]

As pcPET radiotracers improve, identification of the origin of PSA relapse is occurring at lower PSA levels than ever before demonstrated. Figure 3 demonstrates that a median of 51.5% of patients have potential sites of recurrence detected when the PSA level is <1.0 ng/mL using Ga-68/F-18 PSMA. The detection rate increases to 74% when PSA rises above 1.0 ng/mL, and surpasses 90% once the PSA level is >2.0 ng/mL. Similar, albeit lower, trends are observed with choline- and fluciclovine-based radiotracers. Sensitive functional imaging has led to patterns of recurrence studies that provide insight into how prostate cancer spreads early on in the process of metastasis in a variety of clinical scenarios including postprostatectomy, post-definitive radiation therapy, and postprostatectomy radiation therapy.[6-8] Patterns of recurrence studies, such as these and others, have prompted further discussion regarding additional local therapy directed to the at-risk nodal basins or aggressive metastasis-directed therapy.

The era of functional imaging has arrived, and clinicians around the globe are using this technology to develop customized radiation therapy plans. In a recent meta-analysis by Ost et al, metastasis-directed therapy to regional and distant recurrences included 66% of patients receiving radiation therapy.[11] The authors found that 51% of patients were progression free 1 to 3 years after salvage metastasis-directed therapy. Toxicity evaluation revealed metastasis-directed radiation therapy was well tolerated, with 8.5% of patients experiencing grade 2 toxicities and 1 case of grade 3 toxicity. Retrospective data coupled with growing experience using pcPET-directed therapy have prompted the development of prospective studies (Table Supplementary Material (PDF); available as supplementary material online only at www.practicalradonc.org). In addition to pcPET-directed external beam radiation therapy, there is also growing experience regarding theranostic applications; the most commonly discussed being lutetium 177 PSMA, which is beyond the scope of this review.

Conclusions

Biochemical recurrence in the prostate cancer patient often presents a therapeutic challenge to the treating oncologist. Data support early intervention with salvage radiation therapy after prostatectomy and argues against prolonged monitoring of detectable postprostatectomy PSA levels.[79,80] Patients in this clinical situation may still benefit from pcPET imaging to identify the area of recurrence, even at very low PSA levels. Furthermore, imaging with both a pcPET scan and a multiparametric MRI scan can provide complementary insight as to the location of recurrence. Not all patients presenting to the treating oncologist fall into this relatively common clinical scenario of a rising PSA early after prostatectomy, however. Indeed, some patients present with rising PSA after definitive radiation therapy, whereas others present after they have received postprostatectomy radiation therapy, and others still after a late PSA rise years after initial surgery. It is within these challenging cases that pcPET imaging has important clinical utility. Review of the current literature generally favors PSMA-based imaging in the setting of biochemical recurrence; nevertheless, more comparative studies are needed to further clarify which pcPET radiotracer is most appropriate in each of a variety of clinical presentations. Functional imaging studies that incorporate genomic profiling may provide additional insight as to which patients will derive the greatest benefit from pcPET imaging and which patients have the most to gain from additional local therapy. Prospective studies are ongoing to assess the efficacy of pcPET-directed local therapy in patients with biochemical failure.

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